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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,127	06/16/2006	Motoyuki Sugai	1680/14	3226

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EXAMINER	
GANGLE, BRIAN J	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,127	SUGAI ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) *3* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/16/2006, 8/13/2009, and 9/2/2009* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 8/13/2009 is acknowledged. Claims 1 and 3 are amended. Claims 1-3 are pending.

Election/Restrictions

Applicant's election of group I (claims 1-2) in the reply filed on 8/13/2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim 3 is withdrawn as being drawn to a nonelected invention. Claims 1-2 are currently under examination.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. However, it is noted that no English language translation of JP 2003-419123 has been provided. Therefore, until such a translation is provided, applicant cannot rely upon the foreign priority papers to overcome the rejections set forth below because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Information Disclosure Statement

The information disclosure statements filed on 6/16/2006, 8/13/2009, and 9/2/2009 have been considered. Initialed copies are enclosed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference

claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of copending Application No. 11/921,876. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending claims are drawn to a bactericide and dental caries prophylactic agent comprising automutanolysin, which has 98.4% sequence homology with the instantly claimed SEQ ID NO:1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a bactericide which contains a protein with the amino acid sequence of SEQ ID NO:1 of which has up to 5% of it's amino acids deleted, substituted, or

added and which has a lytic activity against *Streptococcus mutans* or *Streptococcus sobrinus*; a protein with a molecular weight between 90 and 110 kDa which lyses killed *Streptococcus mutans* in a zymography; or a protein obtained from cultured cells transformed by DNA comprising a nucleotide sequence of SEQ ID NO:2 or DNA encoding said protein.

The claims encompass a vast genus of proteins, including those with 95% sequence homology to SEQ ID NO:1, any protein that is capable of lysing *S. mutans* and which has a molecular weight between 90 and 110 kDa, and any protein produced by a cell that has been transformed by DNA comprising a nucleotide sequence of SEQ ID NO:2. Section (3) of claim 1 is not limited to the actual protein produced by the DNA used to transform the cell, but instead includes *any* protein produced by the transformed cell. In addition, the DNA used to transform the cell includes *any* nucleotide fragment of SEQ ID NO:2, which includes almost every protein known to man. Each of the proteins must be bactericidal against *S. mutans* or *S. sobrinus*. In addition, for claim 2, the protein must be preventive and therapeutic for tooth decay, which means that the protein must be capable of entirely preventing tooth decay and capable of repairing damage done by previous tooth decay.

The specification discloses a single protein with the sequence of SEQ ID NO:1, which is encoded by the sequence of SEQ ID NO:2. Said protein is able to lyse *S. mutans* and *S. sobrinus*, though it is less effective against viable cells than it is against cells killed by boiling. There is a lack of any evidence to show that the protein is capable of killing cells during *in vivo* use or that it prevents tooth decay or repairs tooth decay. Thus, there is no guidance with regard to what proteins are capable of performing the required function, which 5% of SEQ ID NO:1 can be altered while retaining the function, or what structural characteristics a protein with the appropriate molecular weight would have.

The peptides have no correlation between their structure and function. The claim requires that the peptide exhibit bactericidal activity as well as preventive and therapeutic effects, but the specification provides no guidance regarding which proteins are capable of the required function. Therefore, the specification provides insufficient written description to support the genus encompassed by the claim. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that

"applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid and/or protein itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404. 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and does so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2datl966.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie *et al.* (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (column 1, page 1306). Bowie *et al.* further teach that while it is known that many amino acid substitutions are possible in any

given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions at all (column 2, page 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess *et al.* (J. Cell Biol. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar *et al.* (Mol. Cell. Biol., 8:1247-1252, 1988) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Additionally, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, column 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, column 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, column 3). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, column 2). Most features predicted with an accuracy of greater than 70% are of structural nature and, at best, only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399, paragraph bridging columns 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those features are missing or predicted wrongly. This has to be kept in mind when processing

the results further (p. 400, paragraph bridging cols 1 and 2). Given not only the teachings of Bowie *et al.*, Lazar *et al.* and Burgess *et al.* but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, the claimed proteins could not be predicted based on sequence identity to SEQ ID NO:1, and especially could not predicted based on a molecular weight with a range of 20,000 daltons. Clearly, it could not be predicted that polypeptide or a variant that shares only partial homology with a disclosed protein will function in a given manner (i.e. serve as a bactericidal compound with preventive or therapeutic effects).

Therefore, only SEQ ID NO:1, but not the full breadth of the claims, meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered vague and indefinite by the phrase "a protein having a 100±10 kDa band of lysed bacteria in a zymography containing killed *Streptococcus mutans*." It is not clear how a protein can have a band in a zymography. There can *be* a band where bacteria are lysed, but the protein does not *have* a band. Likewise, it is not clear how a band can have a molecular weight.

Claim 1 is rendered vague and indefinite by the phrase "DNA encoding said protein(1)." It is not clear which protein this refers to. Section (3) of the claim begins with "a protein." Is this "said protein" or does the "(1)" mean that "said protein" is the protein of section (1)?

Claim 2 is rendered vague and indefinite by the phrase "preventive agent of tooth decay , a therapeutic agent of tooth decay, a toothpaste, an oral cavity cleaner or a preventive gum of tooth decay." An "agent of tooth decay" would be an agent that causes tooth decay. A "preventive" agent of tooth decay must be preventive, but it would still be an agent that causes tooth decay; thus, it is not clear what is preventive. The same issue exists for therapeutic agents of tooth decay and gums of tooth decay.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 rejected under 35 U.S.C. 102(a) as being anticipated by Yoshimura *et al.* (Microbiol. Immunol., 48:465-469, June, 2004; IDS filed 8/13/2009).

The instant claims are drawn to a bactericide against *Streptococcus mutans* and *Streptococcus sobrinus* comprising a protein with the sequence of SEQ ID NO:1 or having up to 5% sequence homology with SEQ ID NO:1 and having a lytic activity against *Streptococcus mutans* or *Streptococcus sobrinus*; a protein with a molecular weight of 90-110 kDa which shows a band of lysed bacteria in a zymography containing killed *Streptococcus mutans*; or a protein encoded by DNA with the sequence of SEQ ID NO:2.

Yoshimura *et al.* disclose a bacteriolytic enzyme from *S. mutans* which creates a band of lysed bacteria in a zymography containing killed *Streptococcus nutans* at 100 kDa (see abstract). Since the Patent Office does not have the facilities for examining and comparing Applicant's composition with the compositions of the prior art reference, the burden is upon Applicant to show a distinction between the material, structural and functional characteristics of the claimed composition and the composition of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Therefore, in the absence of evidence to the contrary, a composition containing said enzyme would be a preventive agent of tooth decay.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claims 1-2 rejected under 35 U.S.C. 102(b) as being anticipated by Wang *et al.* (WO 02/077183A2, 2002; IDS filed 9/2/2009).

The instant claims are drawn to a bactericide against *Streptococcus mutans* and *Streptococcus sobrinus* comprising a protein with the sequence of SEQ ID NO:1 or having up to 5% sequence homology with SEQ ID NO:1 and having a lytic activity against *Streptococcus mutans* or *Streptococcus sobrinus*; a protein with a molecular weight of 90-110 kDa which shows a band of lysed bacteria in a zymography containing killed *Streptococcus mutans*; or a protein encoded by DNA with the sequence of SEQ ID NO:2.

Wang *et al.* disclose a composition comprising a pharmaceutically acceptable carrier and a purified protein produced from a cell transformed with SEQ ID NO:36377, which contains a nucleotide sequence of the instantly claimed SEQ ID NO:2 (see page 14, lines 27-30 and page 137, lines 34-36) (nucleotides 1-240 of SEQ ID NO:36377 match of nucleotides 2161-2400 of SEQ ID NO:2). Since the Patent Office does not have the facilities for examining and comparing Applicant's composition with the compositions of the prior art reference, the burden is upon Applicant to show a distinction between the material, structural and functional characteristics of the claimed composition and the composition of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Therefore, in the absence of evidence to the contrary, a composition containing said enzyme would be a preventive agent of tooth decay.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571)272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian J Gangle/
Examiner, Art Unit 1645

/Robert B Mondesi/
Supervisory Patent Examiner,
Art Unit 1645